MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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SUBJECT: BRIEFING DOCUMENT
Drugs: Acetaminophen-Containing Products
Safety Issue: Hepatotoxicity

EXECUTIVE SUMMARY

This document provides a summary of our analysis of 307 US cases of liver injury reported in association with ingestion of one or more acetaminophen-containing drug products received by the Agency from 1998 to July 2001. Our objective was to determine the circumstances, which led to hepatotoxicity. Although we excluded cases with obvious evidence of suicidal intention, we cannot completely rule out the possibility that some cases may have been suicide-related. Twenty-five cases involved pediatric patients and 282 cases involved adults and patients greater than 12 years of age. All cases were categorized into liver injury categories as defined later in this document. For both the pediatric and adult cases, 60% were categorized with severe life threatening liver injury and liver failure. Fatalities occurred in approximately 40% of all patients.

For the pediatric patients, males represented 60% of the cases reviewed. Single ingredient acetaminophen or an unspecified acetaminophen product was most commonly implicated. The product reported most frequently was an acetaminophen concentrated liquid formulation (100mg/ml). Most patients were receiving only one OTC single ingredient acetaminophen-containing product. Potential contributing factors or confounders were noted in 10 cases. Eighty-four percent of the pediatric cases involved medication errors. Up to 15 patients received an improper dose secondary to use of an improper measuring device, misinterpretation of label dosing guidelines or instructions provided by a health care provider (HCP), or confusion over differing acetaminophen product concentrations (i.e., use of acetaminophen concentrated drops (100 mg/ml) were used instead of acetaminophen suspension (32 mg/ml)). Four were classified as

accidental ingestion of an acetaminophen-containing product and five were possibly due to forced ingestion (two possible child abuse and three involved fetal exposure to acetaminophen by maternal ingestion). There were four cases that did not convey information that would suggest that a medication error resulted in acetaminophen-associated hepatotoxicity. Three of the four cases reported co-suspect medications that might have contributed to the event.

For the adult patients, females represented just over 60% of the cases reviewed. The ages ranged from 15 to 85 years old. Of all adult patients the mean and median daily dose was 6.5 and 5 gm/day, respectively. The median daily dose in grams increased with the severity of the hepatic injury. Overall, 41% provided information to suggest that > 4 grams per day was ingested, 22% provided information to suggest that </= 4 grams per day was ingested, and 37% did not provide any dosing information.

Most cases listed an unspecified acetaminophen product. The next highest categories involved the use of RX combination products with narcotics and OTC single ingredient products listed in 122 and 76 cases, respectively. Where the dosage strength was determined, 500mg acetaminophen-containing products appeared to be the most implicated. Approximately 25% of all individuals took more than one acetaminophen-containing product with higher percentages in hepatic injury categories 4 and 2. Of the 58 cases that involved the use of two acetaminophen-containing products, the combined use of an RX combination product with narcotic and an unspecified APAP product or single ingredient APAP product occurred most frequently. Potential contributing factors or confounders were noted in many adult cases (62%). These include ethanol use in 41%, underlying liver disease in 25%, and use of potentially hepatotoxic co-suspect medication in 22%. (4). In general, the daily dose of acetaminophen for individuals with potential contributing factors was lower which suggests that acetaminophen doses required to produce liver injury may be lower in individuals with one or more of these factors.

In summary, use of higher than the recommended dose of acetaminophen occurred more often than did use of recommended doses or less for both the pediatric and adult cases. For the pediatric cases, administration of higher than the recommended dose appeared to occur as a result of parents or caregivers misunderstanding either the label or what was conveyed to them by a HCP and/or product confusion. Additionally, there were cases of forced ingestion and accidental ingestion by a child that may have resulted in higher than the recommended doses of acetaminophen. The motive for taking higher than the recommended doses in the adult cases is unknown.

INTRODUCTION

Using the AERS data to enumerate cases of hepatotoxicity associated with acetaminophen-containing products is problematic for a couple of reasons. Adverse event reporting is voluntary and is associated with significant underreporting. This is compounded by the fact that there is no requirement for sponsors of OTC monograph products to submit adverse event reports to the Agency. For these reasons we are unable

to determine the incidence of hepatotoxicity associated with acetaminophen by spontaneous reports.
Our objective was to review the more recent cases (since 1998) to describe the characteristics or the circumstances which might have led to hepatotoxicity.

CASE DEFINITIONS

The following case definitions were developed by John Senior M.D. and David Graham M.D. and were used to categorize the extent of liver injury.

Category 1: Very Mild or Poorly characterized liver injury - Serum ALT or AST elevated but <3 x ULN; normal total bilirubin and prothrombin time (PT).

Category 2: Mild to Moderate Liver injury - serum transaminase elevations with no evidence of overall liver function loss. This may also include reports of hepatitis NOS, with no lab data and reports of elevations in transaminases w/o signs or symptoms of overall loss of liver function. Further sub-categorization can be determined using the following:

A. Mild: At least 3 x ULN ALT or AST but <10x ULN; normal bilirubin and PT.
B. Moderate: At least 10 x ULN ALT or AST; normal bilirubin and PT.

Category 3: Moderately severe and potentially threatening - liver injury causing acute impairment of liver function w/inability to make enough PT or clear bilirubin from the blood sufficiently. Impaired liver function without liver failure. Reported clinical signs or symptoms might include jaundice, coagulopathy, and elevated bilirubin. Further sub-categorization can be determined using the following:

A. Possibly threatening: At least 3x ULN ALT or AST and (elevation of bilirubin to <3 x ULN or PT (INR) to < 1.5).
B. Definitely threatening: At least 3x ULN ALT or AST and INR > 1.5 or bleeding events (hematuria, bleeding gums, etc.), or jaundice or elevation of bilirubin to at least 3 x ULN

Category 4: Severe life threatening injury w/liver failure - severe liver injury with secondary impairment of brain or kidney function. In the setting of acute hepatic disease (see 3B), altered mental status, decreased consciousness, encephalopathy or coma; or reduced kidney function (SCr >3 mg/dL, or hepatorenal syndrome); being placed on liver transplant list, transplantation, or death. The biggest distinction b/n 3 and 4 is neurologic and kidney involvement. This will also include reports with a diagnosis of liver failure without supporting clinical or laboratory data.

METHODS

Several safety evaluators reviewed AERS case reports and entered findings in an Access database. A list of the contributors is included as appendix 1. The reviewers were instructed to categorize the cases based on available information. For instance, if a case did not provide laboratory information, but stated that the patient was jaundiced and had

hepatic encephalopathy, this case would have been classified as hepatic injury category 4. Analyses were performed using SAS with assistance from Allen Brinker, M.D.

Search Criteria

We conducted a search of the FDA Adverse Event Reporting System (AERS), AERS Datamart, and the published literature for US cases of hepatic injury reported with acetaminophen or acetaminophen-containing products. Our search was limited to cases submitted to the Agency or published between January 1, 1998 to July 25, 2001.

The following terms were used to conduct the AERS and AERS Datamart searches:

HLGT hepatic disorders (exc neoplasms)
HLGT hepatobiliary investigations
PT liver transplant
PT hepatic encephalopathy
PT hepatic necrosis

Search Results

Although our searches with regard to case retrieval and review were limited to cases submitted between January 1998 to July 31, 2001, we provide below crude numbers of all reports in the AERS database.

Crude count of US and Foreign reports of at least one hepatic event that was attributed to acetaminophen and/or other suspect agents (AERS)	1895
Crude count of US reports of at least one hepatic event that was attributed to acetaminophen and/or other suspect agents up to July 31, 2001 (AERS)	1276
Crude count of US reports of at least one hepatic event that was attributed to acetaminophen and/or other suspect agents from January 1, 1998 to July 25, 2001 (AERS and Datamart)	633

Inclusion and Exclusion Criteria for in-depth Analysis

Of the 633 reports, 43 were identified as duplicates for a total of 590 cases. Of these 283 were excluded from in-depth analysis. The inclusion and exclusion criteria are provided below.

Criteria for inclusion of cases (307)

- US cases of liver injury reported in association with consumption of one or more acetaminophen-containing drug products.

Criteria for excluding cases for further review or analysis (283)

- Foreign reports not flagged as foreign in the search (21)
- Reports of suicidal intent or highly suspicious for suicidal intent (167) – reports of suicide attempt or completed suicide as well as those that reported large one time

doses without a therapeutic indication (such as toothache) or those with a narrative stating that patients had psychiatric follow up.

- Reports with co-suspect medications that are known hepatotoxins (22) – that is, three products that were completely are partially withdrawn from the market secondary to hepatic toxicity, trovafloxacin (1), bromfenac (17), and troglitazone (4).
- Reports with greater than two non-APAP co-suspect medications (16) – reports can contain an infinite number of acetaminophen containing products but if greater than two non-APAP products were also temporally related to hepatotoxicity, then these cases were excluded.
- Literature reports describing cases in a tabular format with no information regarding dose or indication (31)
- Reports with no clear liver adverse event (22)
- Reports with products not found to contain acetaminophen (4)

SUMMARY OF PEDIATRIC CASES

Twenty-five cases involved pediatric patients less than or equal 12 years of age. One was published in the medical literature.[1] As would be expected, none of the cases appeared to be intentional suicides. There were two cases where child abuse was in question by the reporter.

Table 1. Selected demographic, outcome, and miscellaneous data in pediatric patients		
Age (n=25):	Range of < 1 day to 8.5 years (mean 2.4 years, median 1.2 years)	
Gender:	Male-17, female-7, unknown-1	
Hepatic Injury Category:	Very mild or poorly characterized liver injury – 4 Mild to moderate liver injury – 3 (2A-2, 2B-1) Moderately severe and potentially threatening – 3 (3A-0, 3B-3) Severe life threatening liver injury w/liver failure - 15	
APAP daily dose:	Ranged from 106 to 375mg/kg/day (n=10)	
Estimated APAP dose (mg/kg/day)	Category 4 4/15	Category 1 to 3 6/10
Mean	252.8	226.3
Median	266.5	228.5
Range	117-361	106-375
APAP indication:	Fever-8, accidental ingestion-4, post-op pain-2, toothache (mother)-2, flu-like symptoms-1, acute illness-1, stomach cramps-1, abdominal pain (mother)-1, unknown-5	
Renal Involvement	Yes-5, Unknown or not reported-20	
Outcomes:	Death-10, Hospitalization-21, ER-2, Required intervention-1	
#APAP Products:	One-22, Two-2, Three-1	
Category of APAP Product:	OTC Single Ingredient Acetaminophen-17 OTC Combination Product-1 Not Specified-11 RX Combination product (w/o narcotic) - 0 RX Combination Product w/Narcotic-1	
Products Identified:	Acetamionphen Concentrated Drops (100mg/ml)-7, Acetaminophen Suspension (32mg/ml)-5, Acetaminophen NOS-11, Unspecified Acetaminophen Chewable-1, Acetaminophen 500mg Adult Strength ,	

	acetaminophen suppository-3, unspecified acetaminophen-containing product with codeine-1, unspecified OTC multi-symptom APAP product-1.
Event year:	prior to 1998-5, 1998-1, 1999-4, 2000-5, 2001-1, not reported-9
Report year:	1998-9, 1999-6, 2000-9, 2001-1
Reporter:	HCP-20, Consumer-4, Attorney-1

The children's ages ranged from less than one-day-old to 8.5 years old. Seventeen were male, seven were female, and there was one patient whose gender was not reported. The hepatic injury category included four with very mild or poorly characterized liver injury, three with mild to moderate liver injury, three with moderately severe and potentially threatening liver injury, and 15 with severe life threatening liver injury with liver failure.

The milligram per kilogram dose was estimated based on reported daily doses and weight and ranged from 106 to 375mg/kg/day (the maximum recommended pediatric dose is 75mg/kg/day). This information could only be estimated in 10 cases. For 12 of 15 remaining cases, dosing information was not provided in eight; reported as normal, recommended, or upper limit of normal in three; and very high in one case. Three cases involving fetal exposure of acetaminophen, reported excessive doses in the mothers, however the amount of acetaminophen that the fetus was exposed to via transmission through the placenta could not be determined. When the daily dose was stratified by hepatic injury category, we noted the mean and median daily dose was higher in children in hepatic injury category 4 compared to the other combined categories, however the number of cases providing dosing information was very small.

Twenty-one children required hospitalization and 10 died. Two children were considered for liver transplantation, however one died prior to the transplant and one recovered. Two children were taken to the emergency department and one reportedly required intervention but none of the three appeared to require extensive intervention besides discontinuation of acetaminophen and laboratory monitoring. Renal involvement was identified in five cases. Involvement included two patients with elevated serum creatinine levels (1.8 and 2.4 mg/dL), one with anuria, and two diagnosed with acute renal failure. All five patients had liver failure (hepatic category 4) and all but one died.

Most patients were receiving an OTC single ingredient acetaminophen or an unspecified acetaminophen product. The product reported most frequently was an acetaminophen concentrated liquid formulation (100mg/ml).. Most patients were receiving only one acetaminophen-containing product (22), however there were two patients receiving two acetaminophen-containing products, and one patient that reportedly was receiving three acetaminophen-containing products. It is not clear whether the use of multiple products led to an overdose of acetaminophen because dosing information was not provided in these cases.

Potential contributing factors or confounders were noted in 10 cases. Six reported one or more co-suspect medications that might have contributed to the event and were started at approximately the same time that the acetaminophen-containing product was started. The medications include azithromycin (2), excessive use of iron (1), ibuprofen, ranitidine (1),

Augmentin (1), cocaine use in mother (1), and amoxicillin. In four cases, underlying liver disease might have contributed. In one case, Hepatitis C antibody was positive, however the reporting physician felt the infant died from high doses of acetaminophen. In another case, the mother had fulminant hepatitis B infection, which was felt to contribute to fetal demise, and in a third case the child had possible TPN-induced liver changes. One child was found to have LCHAD (Long-chain 3-hydroxyacyl-CoA Dehydrogenase) deficiency, which was felt to contribute to his liver failure.

Circumstances Surrounding Acetaminophen Hepatotoxicity

Eighteen cases involved medication errors and three possibly involved medication errors. Medication errors were classified into the categories described below. More than one error may have occurred per case; for example an individual that received the wrong formulation may have also received an improper dose.

- **Improper Dose (15)** –In 13 cases, doses higher than the "recommended daily doses" were reported. Ten cases involved hepatotoxicity in children that occurred at doses above the recommended dose of 75mg/kg/day. Three additional cases did not provide mg/kg doses but reported "very high doses" in one, excessive use in second case, and the use of three different acetaminophen-containing products in the third. In three cases involving adult pregnant women (described below under forced ingestion), doses exceeded the recommended daily adult dose of 4gm/kg/day. Some of these cases overlap with cases summarized in the other medication error categories (wrong formulation-3, accidental ingestion-2, forced ingestion-3). Four cases specifically reported that teaspoonfuls of medication were administered instead of dropperfuls. Some cases pointed out that the dosing error occurred either because the parent misunderstood the label instructions (2) or they misunderstood the instructions provided by the health care provider (3).

- **Wrong Formulation (3)** - In three cases, acetaminophen concentrated drops (100 mg/ml) were used instead of acetaminophen suspension (32 mg/ml) resulting in an overdose of acetaminophen. In two of the three cases, the health care provider specified an exact dose that the parent was to administer, however the dosing recommendations were meant for the less concentrated formulation. In the third case, the details regarding error were not provided.

- **Accidental Ingestion (4)** - Four cases were classified as accidental ingestion of an acetaminophen-containing product. Three children ingested acetaminophen products while the baby sitter was sleeping. Two involved a set of 5-year-old twin girls who ingested an unknown amount of acetaminophen suspension. Both girls were taken to the emergency room and their transaminase levels were elevated, but neither exhibited any symptoms. Two involved accidental ingestion of an amount that is known to be higher than the recommended daily dose of 75mg/kg/day. One involved a 4-year-old female who ingested approximately ½ of a bottle of acetaminophen suspension (1920mg or 105mg/kg). She was hospitalized and treated with N-acetylcysteine and reportedly recovered. One

involved a 3-year-old boy who accidentally ingested 163mg/kg/day of an unspecified acetaminophen product. He reportedly was hospitalized with a peak AST of 966 U/L. No additional information was provided.

- **Forced Ingestion (5)** - Two cases of liver injury were felt to be due to child abuse by the individuals reporting the events. The actual dose could not be determined by the information provided. The possibility of child abuse was considered in a 3-year-old boy because the child had multiple bruises and the presence of opiates in the urine. Further history also disclosed that the child had been given both over-the-counter and prescription formulations containing acetaminophen. In the second case, a police investigator reported possible abuse in an 8-year-old boy. The parents reported administering "recommended doses" of an acetaminophen chewable product. Fifteen hours after admission, the child's acetaminophen level was still in the toxic range. Three cases involved fetal exposure to acetaminophen by maternal ingestion. In all three cases, the mothers took excessive doses of acetaminophen (6gm/day, 8gm/day and 10gm/day) during their pregnancy (25th week, 29th week and 30th week gestation). Two took acetaminophen to treat a toothache and the third took acetaminophen for abdominal pain. Two of the mothers had also taken cocaine in and around the time of the acetaminophen overdose. Two of the infants died and one reportedly recovered.

- **Medication Error NOS (1)** – An 18-month-old child reportedly died as a result of a medication error related to the use of an unknown acetaminophen product. The dose and duration however were not reported, neither were the circumstances describing the medication error.

There were four cases that did not convey information that would suggest that a medication error resulted in acetaminophen-associated hepatotoxicity. In one case a pharmacist reported that an 11-month-old developed liver failure while taking the "normal dose per weight" of an unknown acetaminophen product. In two cases, azithromycin was reported as cosuspect and acetaminophen doses were not provided. In the fourth case, an 8.5-year-old with cerebral palsy and seizure disorder, developed liver failure and died following the use of acetaminophen for fever. She was on numerous concomitant medications including Augmentin and Phenytoin.

SUMMARY OF ADULT CASES

Two hundred eighty-two (282) cases involved adult patients who experienced liver injury possibly associated with the use an acetaminophen-containing product.

Table 2. Selected demographic, outcome, and miscellaneous data in adult patients	
Hepatic Injury Category:	Poorly characterized/very mild liver injury – 42 Mild to moderate liver injury – 29 (2A-11, 2B-18)

	Moderately severe and potentially threatening – 42 (3A-8, 3B-34) Severe life threatening liver injury w/liver failure - 169			
Age (n=254):	Range of 15 to 85 years (mean 43.7 years, median 42 years)			
Age by hepatic injury category	Category 4	Category 3	Category 2	Category 1
	(n=154)	(n=42)	(n=27)	(n=31)
Median	41	41	50	45
Mean	42.7	42.6	48.5	46.2
Range	15-84	15-85	17-76	16-80
Gender:	Male-100, Female-175, Unknown-7			
Gender by hepatic injury category	Category 4	Category 3	Category 2	Category 1
Female	113 (66.9)	21 (50.0)	14 (48.3)	27 (64.3)
Male	53 (31.3)	21 (50.0)	14 (48.3)	12 (28.6)
Not stated	3 (1.8)	0	1 (3.4)	3 (7.1)
Outcomes:	Death-124, Hospitalization-229, Liver Transplant-7			
Outcome by hepatic injury category	Category 4	Category 3	Category 2	Category 1
Hospitalization				
Yes	153 (90.5)	38 (90.5)	21 (72.4)	17 (40.4)
No or not reported	16 (9.5)	4 (9.5)	8 (27.6)	25 (59.5)
Liver transplant				
Yes	7 (4.1)	0	0	0
No or not reported	162 (95.9)			
Death				
Yes	124 (73.4)	0	0	0
No or not reported	45 (26.6)			
Indications for use:	Pain-165, Cold/flu symptoms-26, intentional abuse-9, sleep-4, miscellaneous-4, not reported-74			
Duration of use:	Short-term-86, Long-term-74, not reported-122			
Year event occurred:	Prior to 1998-96, 1998-27, 1999-47, 2000-44, 2001-11, not reported-57			
Year received by FDA:	1998-94, 1999-95, 2000-65, 2001-28			
Reporter:	HCP-202, Consumer or family member-43, Attorney-30, unknown-7			
Reporter by hepatic injury category	Category 4	Category 3	Category 2	Category 1
Consumer/Fam Member	14 (8.3)	3 (7.1)	1 (3.5)	25 (59.5)
HCP	123 (72.8)	37 (88.1)	27 (93.1)	15 (35.7)
Attorney	27 (16.0)	2 (4.8)	0	1 (2.4)
Unknown	5 (2.9)	0	1 (3.5)	1 (2.4)

Approximately 60% of the cases were categorized as liver failure (hepatic injury category 4). The patients' ages ranged from 15 to 85 years old. Females represented just over 60% of the cases reviewed. The mean and median ages by hepatic injury category were similar among patients in categories 3 and 4 and slightly higher among patient in categories 1 and 2. There were approximately twice as many women as men in categories 1 and 4. Gender was approximately equal for the other two categories.

Two hundred twenty-nine patients required hospitalization and 124 died. At least 29 were considered, transferred, or evaluated for liver transplantation. Of these seven received a liver transplant, 11 died prior to transplant, and 11 were lost to follow-up. The higher percentage of serious outcomes in categories 3 and 4 are not surprising.

Almost 60% of individuals were taking an acetaminophen-containing product for analgesia. There were a slightly higher number of individuals that took the products on a short-term basis versus long-term use. Short-term use was defined as less than or equal to 7 days. Ninety-six cases involved adverse events that occurred prior to 1998 spanning from 1976 to 1997; all cases were received by the Agency between 1998 to 2001. Most cases (72%) were reported by a health care professional. Most of the consumer reports were classified in category 1.

The DOTCDP was interested in the cases of renal impairment or failure associated with the use of acetaminophen-containing products. Renal involvement was identified in 99 cases. Involvement included either a diagnosis of Hepatorenal Syndrome, Acute Renal Failure, requirement for dialysis, a serum creatinine >/= 1.5 mg/dL, or a BUN of >/= 20mg/dL.

Table 3. Dosing Information				
Estimated APAP daily dose (n=123):	Ranged from 0.65 to 30 gm/day (mean 6.5gm/day, median 5 gm/day)			
Estimated weight based dose (n=48)	Ranged from 9.6 to 385mg/kg/day (mean 107 mg/kg/day, median 83mg/kg/day)			
Estimated APAP dose (gm/day)	Category 4	Category 3	Category 2	Category 1
	61/169	27/42	14/29	21/42
Mean	7.4	6.2	4.5	5.8
Median	6.0	5.85	4.2	4
Range	0.65-30	1.09-14.5	0.98-11.7	1-22.5
Dose > 4gm/day	Yes (74) or Suggestive of yes (40) – **114** , No (43) or Suggestive of no (18) - **61**, Undeterminable - **107**			
Dose > 4gm/day	Category 4	Category 3	Category 2	Category 1
Yes	39 (23.1)	19 (45.2)	7 (24.1)	9 (21.4)
Suggestive of yes	32 (18.9)	0	4 (13.8)	4 (9.5)
No	20 (11.8)	5 (11.9)	7 (24.1)	11 (26.2)
Suggestive of no	6 (3.6)	5 (11.9)	3 (10.3)	4 (9.5)
Undeterminable	72 (42.6)	13 (31.0)	8 (27.6)	14 (33.3)

In general acetaminophen dose was difficult to determine in many of the cases. The daily dose in grams per day was estimated in 124 of the 282 cases and ranged from 650mg per day to 30gm per day. The mean and median daily dose of 6.5 and 5 gm/day, respectively, are higher than the recommended daily adult dose of most acetaminophen-containing products of 4gm/day. Weight-based dose was estimated in 48 cases and ranged from ~10 to 385mg/kg/day. When the daily dose was stratified by hepatic injury category, we noted the median daily dose in grams increased with hepatic injury score, which is what one might expect.

Thirty-eight percent of the cases provided no dosing information with the highest percentage of these residing in hepatic injury category 4 (42.6 %). One hundred fourteen cases provided quantitative or qualitative information to suggest that the recommended adult dose of 4gm per day was exceeded. Sixty-one cases provided qualitative or quantitative information to suggest that the patients took less than or equal to 4gm per day. For those cases that reported hepatic toxicity in association with less than or equal to the 4gm per day, 26 were categorized in hepatic injury category 4. Of these, 18 reported other factors such as underlying liver disease, ethanol abuse, or other medications.

Table 4. Acetaminophen (APAP) Product Information

Category of APAP Products (number of total mentions = 365):	Unspecified APAP product (APAP NS) - 138 RX Combination Product w/Narcotic (RX combo w/narc) - 122 OTC Single Ingredient APAP (SI APAP) - 76 OTC Combination Product (OTC combo) - 27 RX Combination product w/o narcotic (RX combo w/o narc) - 2			
Dosage Strengths (OTC and RX)	250mg-1, 325mg products-59, 500mg products-119, 650mg products-14, 750mg-7, unknown or not sure-165			
# APAP Products:	One-212, Two-59, Three-9, Four-2			
Dose by # of products	One (n=92)		Two or More (n=31)	
	Mean 6.2 gm/day Median 4.8 gm/day		Mean 10.4 gm/day Median 6.0 gm/day	
# APAP products	Category 4	Category 3	Category 2	Category 1
1	123 (72.8)	33 (78.6)	20 (69.0)	36 (85.7)
2	39 (23.1)	8 (19.0)	7 (24.1)	5 (11.9)
3	7 (4.1)	1 (2.4)	0	1 (2.4)
4	0	0	2 (6.9)	0
Cases listing 2 APAP products (n=58)	RX combo w/narc + APAP NS – 28 cases RX combo w/narc + SI APAP – 12 cases OTC Combo + SI APAP - 8 cases All Other combinations – 11 cases			
Cases listing 3 and 4 APAP products (n=11)	Four RX combo w/narc – 1 case Three RX combo w/narc – 2 cases Three RX combo w/narc + SI APAP – 1 case Two RX combo w/narc + APAP NS – 3 cases Two RX combo w/narc + OTC combo – 1 case One RX combo w/narc + OTC combo + APAP NS – 1 case One RX combo w/narc + OTC combo + SI APAP – 1 case Two OTC combo + SI APAP – 1 case			

Products were grouped into five categories as listed in table 4. Most cases listed an unspecified APAP product. For these products the strength and/or formulation was unknown. The next highest categories involved the use of RX combination products with narcotics and OTC single ingredient products listed in 122 and 76 cases, respectively. Where the dosage strength was determined, 500mg acetaminophen-containing products appeared to be the most implicated.

Most individuals were taking one acetaminophen-containing product. The mean and median daily dose of acetaminophen for individuals taking two or more products was

higher than of those taking only one product. Approximately 25% of all individuals took more than one acetaminophen-containing product with higher percentages in hepatic injury categories 4 and 2. Of the 59 cases that involved the use of two acetaminophen-containing products, the combined use of an RX combo w/narc and an APAP NS product or SI APAP product occurred most frequently (28 and 12 cases, respectively). The use of two OTC formulations (OTC combo and SI APAP) was mentioned in only eight cases. Of the 11 cases involving the use of three and four acetaminophen-containing products, all but one listed the use of one or more RX combo w/narc (one-2, two-4, three-3, four-1).

Table 5. Contributing Factors				
Ethanol Use	Yes-116, No-21, Not reported-145			
Dose of APAP by ETOH Use	Yes (n=49)		No or not reported (n=74)	
	Mean 5.7gm/day Median 4.55 gm/day		Mean 7.1gm/day Median 5.8 gm/day	
ETOH use by hepatic injury category	Category 4 (n=169)	Category 3 (n=42)	Category 2 (n=29)	Category 1 (n=42)
Yes	84 (49.7)	18 (42.9)	8 (27.6)	6 (14.2)
Not reported	77 (45.6)	19 (45.2)	15 (51.7)	34 (80.9)
No	8 (4.7)	5 (11.9)	6 (20.7)	2 (4.8)
H/O or underlying liver disease	Yes-48, Possible-22, No-23, Not reported-189			
Dose of APAP by Liver Dz	Yes or Possible (n=35)		No or Not reported (n=88)	
	Mean 5.8 gm/day Median 4 gm/day		Mean 6.8 gm/day Median 5.65 gm/day	
H/O of liver dz by hepatic injury category	Category 4 (n=169)	Category 3 (n=42)	Category 2 (n=29)	Category 1 (n=42)
Yes and possible (n=70)	46 (27.2)	12 (28.6)	6 (20.7)	6 (14.3)
No and Not reported (n=212)	123 (72.8)	30 (71.4)	23 (79.3)	36 (85.7)
Co-Suspect Medications	**Yes-93, No-189**			
# of Cases with potentially hepatotoxic co-suspect medications-63				
Dose of APAP by potentially hepatotoxic meds	Yes (n=25)		No or not reported (n=97)	
	Mean 5.34gm/day Median 3.9 gm/day		Mean 6.76.1gm/day Median 5.7 gm/day	

Ethanol Use

One hundred sixteen or 41% of the cases mentioned a history of ethanol use. In 103 cases ethanol use was broadly described as alcoholism or ethanol abuse (64), regular or daily use (20), moderate use (3), occasional use (10), and previous use (6). Ethanol use in 15 cases was not well described. Forty-eight of the 116 cases also provided information that suggested that ethanol was used at or about the same time as the acetaminophen was being used.

The mean and median dose of acetaminophen was lower in individuals who reported ethanol use in comparison to those that either did not report ethanol use or reported a

negative ethanol history. This supports the premise that individuals who use ethanol may be more susceptible to liver injury with lower doses of acetaminophen.[2-7] When we stratified ethanol use by hepatic injury category we noted that 88% (102/116) of ethanol users suffered category 3 or 4 liver injury. Of the 64 individuals previously described as alcoholics or ethanol abusers, 50 developed liver failure while taking an acetaminophen-containing product.

Underlying or History of Liver Disease

Seventeen percent of the patients had a history of liver disease or underlying liver disease and 7.6% possibly had a history of or underlying liver disease. The mean and median dose of acetaminophen was lower in individuals with a history of liver disease in comparison to those with no liver disease history. When we stratified liver disease history by hepatic injury category we noted that 83% (58/70) of individuals with underlying or history of liver disease suffered category 3 or 4 liver injury. The liver history ranged from jaundice as an infant and elevated liver function tests to cirrhosis and end stage liver disease. For a more detailed description of the liver history please see appendix 2.

Of those with a history of underlying liver disease, 20 were probably related to ethanol use and one was felt to be due to pain reliever abuse. Twenty-nine reported a history of viral hepatitis or serology possibly consistent with viral hepatitis. The origin of liver disease was not reported in 18 cases and possibly due to congestive heart failure in one patient.

Co-suspect or Concomitant Medications

Ninety-three cases listed one or more co-suspect medications. A total of 74 different medication were identified, of which 64 are labeled for hepatotoxic events and ten actually have warnings or precautions regarding their potential to cause hepatic failure. These 64 potentially hepatotoxic medications were reported in 63 cases. The mean and median dose of acetaminophen was lower in individuals on potentially hepatotoxic co-suspect medication in comparison to those that were not. However, only 40% of these cases provided dosing information. It is unclear whether the co-suspect medications were contributing factors, solely related, or not causally related to the hepatic event.

One hundred thirteen cases listed one or more concomitant medications. Concomitant medications are generally not felt to be as temporally related to the onset of the event as the suspect drugs because many are long term or maintenance medications. Nonetheless, some are labeled for hepatotoxic reactions and it is unknown whether the combined use of these products with acetaminophen contributed to the event. A comprehensive list of all medications (co-suspect and concomitant) is provided as appendix 3.

It is also important to keep in mind that many of the acetaminophen-containing products are combination products with one or more non-acetaminophen ingredients. It is unknown what role these ingredients might have had in the hepatotoxic event.

Summary of all Contributing or Risk Factors

Of the 282 adult cases reviewed, 107 had no identifying risk factors for liver toxicity other than their exposure to the acetaminophen-containing product. Possible risk factors including a history of ethanol use, preexisting or underlying liver disease, and/or a co-suspect medication that is labeled for hepatotoxicity were identified in the remaining cases. One hundred twelve patients had one risk factor, 51 had two risk factors, and 12 patients had three.

DISCUSSION/CONCLUSION

We evaluated 307 US cases of liver injury reported in association with ingestion of one or more acetaminophen-containing drug products received by the Agency between January 1, 1998 to July 31, 2001. These include cases of unintentional overdose, accidental overdose, therapeutic error, abuse and misuse, or those where intention was unknown. Although these cases had no obvious evidence of suicidal intention, we cannot completely rule this out. Twenty-five cases involved pediatric patients less than or equal 12 years of age and 282 cases involved adults and patients greater than 12 years of age.

For both the pediatric and adult evaluations, 60% of patients were categorized with severe life threatening liver injury and liver failure or Hepatic Injury Category 4. Fatalities occurred in approximately 40% of all patients.

For the pediatric patients, males represented 60% of the cases reviewed. An OTC single ingredient acetaminophen or an unspecified acetaminophen product was most implicated. The product reported in most cases was an acetaminophen concentrated formulation. Most patients were receiving only one acetaminophen-containing product (22), however there were three patients that received two or more acetaminophen-containing products. Potential contributing factors or confounders were noted in 10 cases. These include co-suspect medication (6), underlying liver disease (4), and a metabolic disorder (1).

Twenty-one pediatric cases involved one or more medication errors (definitely-18, possibly-3). Up to 15 patients received an improper dose or doses higher than the "recommended daily dose". Four cases specifically reported that teaspoonfuls of medication were administered instead of dropperfuls. Some cases pointed out that the dosing error occurred either because the parent misunderstood the label instructions (2) or they misunderstood the instructions provided by the health care provider (3). In three cases, acetaminophen concentrated drops (100 mg/ml) were used instead of acetaminophen suspension (32 mg/ml). Four were classified as accidental ingestion of an acetaminophen-containing product. Two cases of liver injury were felt to be due to child abuse by the individuals reporting the events. Three cases involved fetal exposure to acetaminophen by maternal ingestion. In all three cases, the mothers took excessive doses of acetaminophen during their pregnancy. There was one case that reported a medication error but did not provide details. There were four cases that did not convey information that would suggest that a medication error resulted in acetaminophen-associated hepatotoxicity. Three of the four cases reported co-suspect medications that might have contributed to the event.

For the adult patients, females represented just over 60% of the cases reviewed. Patients in hepatic injury categories 3 and 4 were slightly younger than those in categories 1 and 2. Of all adult patients (where dose was provided), the mean and median daily dose was 6.5 and 5 gm/day, respectively. The median daily dose in grams increased with hepatic injury score. Overall, 41% provided information to suggest that > 4 grams per day was ingested, 22% provided information to suggest that </= 4 grams per day was ingested, and 37% did not provide any dosing information.

Most cases listed an unspecified APAP product. The next highest categories involved the use of RX combination products with narcotics and OTC single ingredient products listed in 122 and 76 cases, respectively. Where the dosage strength was determined, 500mg acetaminophen-containing products appeared to be the most implicated. Approximately 25% of all individuals took more than one acetaminophen-containing product with higher percentages in hepatic injury categories 4 and 2. Of the 59 cases that involved the use of two acetaminophen-containing products, the combined use of an RX combination product with narcotic and an unspecified APAP product or single ingredient APAP product occurred most frequently. Potential contributing factors or confounders were noted in many adult cases. These include ethanol use in 41%, underlying liver disease in 25%, and use of potentially hepatotoxic co-suspect medication in 22%.

In summary, use of higher than the recommended dose of acetaminophen occurred more often than did use of recommended doses or less for both the pediatric and adult cases. For the pediatric cases, administration of higher than the recommended dose appeared to occur as a result of parents or caregivers misunderstanding either the label or what was conveyed to them by a HCP and/or product confusion. Additionally, there were cases of forced ingestion and accidental ingestion by a child that may have resulted in higher than the recommended doses of acetaminophen. The motive for taking higher than the recommended doses in the adult cases is unknown but may be related to individuals either not being unaware of the potential toxicity associated with the use of acetaminophen or the use of multiple products containing acetaminophen.

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Appendix 1. The following individuals contributed towards the methodology, review, or analyses of the AERS data.

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Appendix 2. Diagnosis of previous liver disease or underlying liver disease of 69 adult patients. (only one diagnosis for each case listed)

Alcoholic hepatitis	2
Alcoholic liver disease	3

Ascites	1
Cirrhosis	12
Elevation in liver enzymes	4
End Stage Liver Disease	2
Hepatic Congestion	1
Hepatic Portal Shunt Operation	1
Hepatitis A	2
Hepatitis B (or serology c/w hep B)	6
Hepatitis B and A	1
Hepatitis B and/or C	5
Hepatitis C (or serology c/w hep C)	8
Hepatitis or viral hepatitis (not otherwise specified)	8
Hepatomegaly	3
Jaundice	1
Liver disease (not otherwise specified)	7
Scherosing Cholangitis	1
Steatosis	1

Appendix 3. Listing of all Co-suspect and Concomitant Medications (alphabetically)

Product	cosuspect	cos #†	conc #‡	Labeled *	labeled hepatic reaction
Acitretin (Soriatane)**	Yes	1	0	y	Clinical jaundice with elevated serum bilirubin and transaminases, cirrhosis noted in clinical trials. Elevations of AST (SGOT), ALT (SGPT), GGT (GGTP) or LDH, clinical or histologic hepatitis, there have been reports of hepatitis-related deaths (W)
Albuterol	No	0	6	n	
Aldactone	No	0	2	y	mixed cholestatic/hepatocellular toxicity (AR)
Allopurinol	No	0	2	y	clinical hepatotoxicity, elevated asymptomatic rises in serum alkaline phosphatase or serum transaminase (W), hyperbilirubinemia, hepatomegaly, jaundice, liver failure (AR)
Alprazolam (Xanax)	No	0	6	y	liver enzyme elevations, hepatitis, hepatic failure, jaundice (AR)
Amitriptyline	No	0	9	y	Rarely hepatitis (including altered liver function and jaundice) (AR)
Amlodipine (Norvasc)	No	0	2	y	Jaundice and hepatic enzyme elevations (mostly c/w cholestasis or hepatitis) (AR)
Amoxicillin	Yes	1	2	y	moderate rise in AST (SGOT) and/or ALT (SGPT), hepatic dysfunction including cholestatic jaundice, hepatic cholestasis and acute cytolytic hepatitis (AR)
Amoxicillin/clavulanic acid (Augmentin)	Yes	1	1	y	hepatic dysfunction (W), Transaminase elevations, hepatic dysfunction rarely leading to death (AR)
Ampicillin	No	0	3	y	Increased AST (SGOT), ALT (SGPT), alkaline phosphatase, and LDH (AR)
Aspirin	Yes	3	10	n	
Atenolol (Tenormin)	No	0	1	n	
Atorvastatin (Lipitor)	Yes	1	2	y	inc LFTs (W, AR) hepatitis,cholestatic jaundice (AR)
Azithromycin (Zithromax)	Yes	3	0	y	Abnormal liver function including hepatitis and cholestatic jaundice, as well as rare cases of hepatic necrosis and hepatic failure, some of which have resulted in death (AR)
Baclofen (Lisersal)	No	0	1	y	Label not readily available, the following information was found in Micromedex: A case of significant increases in ALT (SGPT) and AST (SGOT) were reported in a 27-year-old male after approximately 6 weeks of baclofen therapy (15 to 80 mg daily)
Beclomethasone (Vanceril)	No	0	2	n	
Benazepril (Lotensin)	No	0	1	y	Class labeling - cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death (W) not specific for benazepril
Benzonatate (Tessalon)	No	0	1	n	
Bisacodyl (Dulcolax)	No	0	2	n	
Bromocriptine	Yes	1	0	n	label not readily available, Micromedex did not list hepatotoxicity
Budesonide (Rhinocort nasal spray)	No	0	1	n	
Bumetanide (Bumex)	No	0	2	y	Alterations in LDH, total serum bilirubin, AST, alkaline phosphatase (0.4%), and ALT have occurred with bumetanide therapy
Buspirone (Buspar)	No	0	1	n	labeling not readily available, no mention of hepatotoxicity in Micromedex
Butorphanol (Stadol)	No	0	1	n	
Caffeine	No	0	1	n	
Calcium carbonate	No	0	1	n	
Carbamazepine (Tegretol)**	Yes	2	2	y	Hepatic effects, ranging from slight elevations in liver enzymes to rare cases of hepatic failure have been reported (AR, P)
Carisoprodol (Soma)	Yes	5	7	n	
Carvedilol (Coreg)	No	0	1	y	hepatic injury described as liver function abnl (W, AR)
Cefadroxil (Duricef)	No	0	1	y	hepatic dysfunction including cholestasis and elevations in serum transaminase, idiosyncratic hepatic failure (AR)
Cefprozil (Cefzil)	No	0	1	y	Elevations of AST (SGOT) (2%), ALT (SGPT) (2%), alkaline phosphatase (0.2%), and bilirubin values (<0.1%), cholestatic jaundice (AR)
Cefuroxime (Ceftin)	No	0	1	y	Hepatic impairment including hepatitis and cholestasis, jaundice, inc LFTs (AR)
Celecoxib (Celebrex)	No	0	1	y	NSAID class labeling - Inc LFT and enzymes, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) (P, AR)
Cetirizine (Zyrtec)	No	0	1	y	cholestasis, hepatitis, abn liver function (AR)
Chlordiazepoxide (Librium)	Yes	1	1	y	jaundice and hepatic dysfunction (AR)

Product	Cosuspect	cos #†	conc #‡	Labeled *	labeled hepatic reaction
Chlorzoxane (Parafon Forte)**	Yes	1	1	y	Serious (including fatal) hepatocellular toxicity has been reported rarely in patients (W)
Choline Magnesium Trisalicylate (Trilisate)	No	0	1	y	elevated hepatic transaminases, hepatitis (AR)
Cisapride (Propulsid)	No	0	1	n	labeling not readily available, no mention of hepatotoxicity in Micromedex
Citalopram (Celexa)	No	0	1	y	Jaundice (AR)
Clarithromycin (Biaxin)	Yes	1	2	y	Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, hepatic failure with fatal outcome (AR)
Clomipramine (Anafranil)	No	0	1	y	CLOMIPRAMINE has induced elevated aspartate aminotransferase (AST or SGOT) and alanine aminotransferase (ALT or SGPT) in approximately 1% and 3% of patients, respectively, to levels 3 times the upper limit of normal (Prod Info Anafranil(R), 1995).
Clonazepam (Klonopin)	No	0	2	y	Hepatomegaly, transient elevations of serum transaminases and alkaline phosphatase (AR)
Clonidine patch (Catapress)	No	0	1	y	mild transient abnormalities in liver function tests, hepatitis w/ oral (AR)
Clopidogrel (Plavix)	No	0	1	y	Bilirubinemia, hepatitis infectious, liver fatty (AR)
Clotrimazole (Mycelex)	No	0	1	y	Abnormal liver function tests have been reported in patients treated with clotrimazole troches; elevated SGOT levels were reported in about 15% of patients in the clinical trials (P)
Cocaine	Yes	2	4	NA	
Cyclobenazprine (Flexeril)	No	0	2	y	abnormal liver function, hepatitis, jaundice, and cholestasis have been reported in less than 1% of patients receiving cyclobenzaprine therapy (Prod Info Flexeril(R), 1996)
Cyclophosphamide (Cytoxan)	No	0	2	y	jaundice (AR)
Cytarabine	Yes	1	0	y	Label not readily available. Micromedex contained the following: JAUNDICE, HYPERBILIRUBINEMIA, and hepatic dysfunction have been reported to occur with cytarabine therapy (Prod Info Cytosar-U(R), 1999), fatal veno-occlusive disease.
Dexamethasone (Decadron)	No	0	2	n	
Dextromethorphan	No	0	1	n	
Diazepam (Valium)	Yes	1	4	y	jaundice (AR)
Diclofenac/misoprostol (Arthrotec)	Yes	1	0	y	NSAID class labeling - elevations of one or more liver tests severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with diclofenac (P, AR)
Digoxin	No	0	2	n	
Dilantin (phenytoin)	Yes	5		y	toxic hepatitis and liver damage (AR)
Diltiazem	No	0	1	y	Mild elevations of transaminases with and w/o concomitant elevation in alkaline phosphatase and bilirubin (W, AR)
Diphenhydramine	Yes	2	2	n	
Dipyridamole (Persantine)	No	0	1	y	rare reports of liver dysfunction, hepatitis (AR)
Disulfiram (Antabuse)	No	0	1	y	Hepatic toxicity including hepatic failure resulting in transplantation or death have been reported, hepatitis (P, AR)
Docetaxel (Taxotere)	Yes	1	0	y	elevations in transaminases, bilirubin, and Alk phos (BB, P, AR)
Docusate Sodium	No	0	1	n	
Donepezil (Aricept)	Yes	1	0	y	increased transaminases, jaundice, hepatitis (AR)
Doxycylcine (Vibramycin)	Yes	1	0	y	hepatotoxicity (AR)
Doxylamine (Unisom)	Yes	1	1	n	
Emetrol	No	0	1	n	
Enalapril (Vasotec)	No	0	4	y	Class labeling: cholestatic jaundice and progresses to fulminant hepatic necrosis, and (sometimes) death (W) Not specific for enalapril
Erythromycin	No	0	1	y	There have been reports of hepatic dysfunction with or without jaundice, occurring in patients receiving oral erythromycin products (W, AR)
Etodolac (Lodine)	Yes	1	0	y	NSAID class labeling - elevations of one or more liver tests, jaundice, severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with etodolac (P, AR)
Famotidine (Pepcid)	Yes	1	1	y	cholestatic jaundice, liver enzyme abnormalities (AR)
Fentanyl (Duragesic) patch or unspecified	No	0	3	n	

Product	Cosuspect	cos #†	conc #‡	Labeled *	labeled hepatic reaction
Fluconazole (Diflucan)**	Yes	2	0	y	Hepatic injury: DIFLUCAN has been associated with rare cases of serious hepatic toxicity, including fatalities primarily in patients with serious underlying medical conditions. (W, AR)
Fludrocortisone (Florinef)	No	0	1	n	label not readily available, Micromedex did not list hepatotoxicity
Flunisolide (Aerobid Inhaler)	Yes	1	2	n	
Fluoxetine (Prozac)	Yes	1	7	y	Infrequent: liver function tests abnormal, Rare: hepatitis, liver fatty deposit (AR)
Fluticasone (Flonase)	No	0	2	n	
Fosinopril (Monopril)	No	0	1	y	Class labeling: cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death (W) not specific for fosinopril
Furosemide	Yes	1	6	y	jaundice (intrahepatic cholestatic jaundice) (AR)
Gabapentin (Neurontin)	No	0	3	y	elevated LFTs, jaundice, hepatomegaly, hepatitis (AR)
Ganciclovir (Cytovene)	Yes	1	0	y	abnormal liver function tests, cholestasis, encephalopathy, hepatic failure, hepatitis (AR)
Gemfibrizol (Lopid)	No	0	1	y	abnormal LFT (P, AR)
Gentamicin	No	0	1	n	labeling not readily available, no mention of hepatotoxicity in Micromedex
Glimepiride (Amaryl)	No	0	1	y	elevation of liver enzyme levels, cholestasis,jaundice, hepatitis, liver failure (AR)
Glipizide (Glucotrol)	No	0	1	y	Cholestatic jaundice may occur rarely with sulfonylureas: GLUCOTROL should be discontinued if this occurs, elevations of SGOT, LDH, alkaline phosphatase, jaundice (AR)
Glucophage (Metformin)	Yes	2	0	y	Impaired hepatic function (P)
Glutethamide	Yes	2	0	n	could not find label, micromedex did not mention hepatotoxicity
Glyburide (DiaBeta, Glucovance)	No	0	2	y	Cholestatic jaundice, hepatitis, liver function abnormalities, including isolated transaminase elevations (AR)
Goldenseal	No	0	1	na	not drug product, Micromedex did not mention hepatotoxicity
Halothane (Fluothane)	Yes	1	0	y	hepatic dysfunction and/or jaundice (W), severe hepatic dy function (including hepatic necrosis) (AR)
Heparin	No	0	1	y	Significant elevations of aminotransferase (SGOT [S-AST] and SGPT [S-ALT])
Hydrochlorthiazide	No	0	5	y	jaundice (intrahepatic cholestatic jaundice) (AR)
Hydroxychlorquine (Plaquenil)	No	0	1	n	
Hyoscyamine (Levsin)	No	0	1	n	
Ibuprofen	Yes	8	7	y	NSAID class labeling - elevations of one or more liver tests, severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ibuprofen(P, AR)
Indinavir (Crixivan)	No	0	1	y	Hepatitis including cases resulting in hepatic failure (W), abn LFT and enzymes (P), liver function abnormalities; hepatitis including reports of hepatic failure, jaundice (AR)
Insulin (reg and NPH)	No	0	8	n	
Ipratropium (Atrovent)	No	0	2	n	
iron sulfate	Yes	1	1	y	label not readily available, according to Rudolph's Pediatrics, 20th edition iron poisoning can cause liver dysfunction.
Isoflurane	Yes	1	0	y	could not find label, micromedex adverse events section outlined increases in hepatic glutathione S-transferase (GST) Massive HEPATIC NECROSIS
isosorbide dinitrate (Imdur)	No	0	1	y	SGOT increase, SGPT increase (AR)
Isotretinoin (Accutane)	Yes	1	0	y	Clinical hepatitis,mild to moderate elevations of liver enzymes (W, P, AR)
Ketoprofen (Oruvail, Orudis)	Yes	1	1	y	borderline elevations of one or more liver function tests (P), hepatic dysfunction, hepatitis, cholestatic hepatitis, jaundice (AR)
Ketorolac (Toradol)	Yes	1	0	y	NSAID class labeling - elevations of one or more liver tests, jaundice, severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with ketorolac (P, AR)
Lamivudine (Epivir)	No	0	1	y	severe hepatomegaly w/steatosis, including fatal case (BB, W, P) abnormal transaminases exaserbation of Hep B (AR)
Lamivudine/Zidovudine (Combivir)**	Yes	1	0	y	severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including lamivudine, zidovudine, and other antiretrovirals (BB, W)
Lansoprazole (Prevacid)	No	0	1	y	hepatotoxicty, elevated LFTs (AR)
Leflunomide (Arava)	Yes	1	0	y	elevation enzymes primarily transaminases (W, AR)
Leuprolide acetate (Lupron)	No	0	1	y	hepatic dysfunction (AR)
Levaquin (levofloxacin)**	Yes	1	0	y	hepatitis; jaundice; acute hepatic necrosis or failure (W), abnormal hepatic function, hepatic coma, jaundice (AR)
Lidocaine	No	0	1	n	

Product	Cosuspect	cos #†	conc #‡	Labeled *	labeled hepatic reaction
Lisinopril (Prinivil)	No	0	4	y	Class labeling - cholestatic jaundice and progresses to fulminant hepatic necrosis and (sometimes) death (W) not specific for lisinopril
Loratadine (Claritin)	Yes	1	0	y	abnormal hepatic function, including jaundice, hepatitis, and hepatic necrosis (AR)
Lorazepam (Ativan)	Yes	1	3	n	
Losartan/Hydrochlorothiazide	No	0	1	y	jaundice, intrahepatic cholestatic jaundice, hepatitis (AR)
Lovastatin (Mevacor)	No	0	1	y	Active liver disease or unexplained persistent elevations of serum transaminases (C) Elevations AST or ALT) (W, P, AR), hepatitis, including chronic active hepatitis, cholestatic jaundice, fatty change in liver; and rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma (AR)
Magnesium sulfate/oxide	No	0	3	n	
Marijuana or THC	No	0	2	na	
Meclizine (Antivert)	No	0	2	n	
Medroxyprogesterone (Provera)	No	0	1	y	cholestatic jaundice
Meperidine	No	0	1	n	
Methadone	No	0	1	y	Label not readily available, the following information was found in Micromedex: METHADONE has been reported to cause hepatotoxicity in at least 3 patients in the literature.
Methocarbamol (Robaxin)	No	0	1	y	jaundice (including cholestatic jaundice (AR)
Methohexital (Brevital)	No	0	1	n	label not readily available, Micromedex did not list hepatotoxicity
Methotrexate	Yes	1	0	y	could not find label, micromedex adverse events section outlined elevated LFTs, hepatitis, cirrhosis, hepatic failure
Metoclopramide (Reglan)	No	0	1	y	jaundice and altered liver function tests, when metoclopramide was administered with other drugs with known hepatotoxic potential (AR)
Metolazone (Zaroxolyn)	No	0	2	y	Hepatitis, intrahepatic cholestatic jaundice (AR)
Metronidazole (Flagyl)	No	0	2	n	
Midazolam (Versed)	Yes	1	0	n	
Morphine	No	0	1	n	
Multivitamin and other vitamins	No	0	1	n	
Nabumetone (Relafen)	No	0	1	y	elevations of one or more liver function tests Severe hepatic reactions, including jaundice and fatal hepatitis, have been reported with Relafen and other NSAIDs. NSAID class labeling (P)
Naldolol (Corgard)	No	0	1	n	labeling not readily available, no mention of hepatotoxicity in Micromedex
Naproxyn	Yes	3	5	y	NSAID class labeling - elevations of one or more liver tests, jaundice, severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with naproxen (P, AR)
Nefazadone (Serzone)	Yes	1	0	y	Abnl liver tests, rare reports of liver necrosis and liver failure, in some cases leading to liver transplantation and/or death. (AR)
Nevirapine (Viramune)**	Yes	1	1	y	Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis and hepatic failure (BB, W, AR)
Nicotine	No	0	1	n	
Nicotinic Acid (aka Niacin,Nicobid)	Yes	1	0	y	label not readily found, the following information was obtained from Micromedex: jaundice, pruritus, nausea, malaise, hepatomegaly, and mild to moderate elevations in serum bilirubin, alkaline phosphatase, and liver enzymes. Isolated cases of fulminant hepatic failure have been reported. Biopsies have revealed hepatic necrosis and lobular collapse, cholestasis, and fibrous formations. Hepatocellular changes have been observed in asymptomatic patients.
Nifedipine (Procardia, Adalat)	No	0	2	y	elevations of enzymes such as alkaline phosphatase, CPK, LDH, SGOT and SGPT have been noted. cholestasis with or without jaundice, allergic hepatitis (P)
Nilutamide (Nilandron)**	Yes	1	0	y	Rare cases of death or hospitalization liver injury. Hepatitis or marked increases in liver enzymes. (W) Enzymes (AR)
Nisoldipine (Sular)	No	0	1	y	Abnormal LFT, hepatomegaly (AR)
Nitroglycerin (Nitrobid)	No	0	1	n	label not readily available, Micromedex did not list hepatotoxicity
OC/HRT	Yes	1	10	n	
Omeprazole (Prilosec)	No	0	4	y	Cholestatic jaundice (AR)
Orphenadrine (Norgesic)	No	0	1	n	
Oseltamivir (Tamiflu)	Yes	1	0	n	

Product	Cosuspect	cos #†	conc #‡	Labeled *	labeled hepatic reaction
Pancrease	No	0	2	n	
Paroxetine (Paxil)	No	0	3	y	liver function tests abnormal, hepatitis, jaundice (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction),(AR)
Penicillin	Yes	2	3	n	
Pepto Bismol	No	0	1	n	
Perphenazine (Trilafon)	No	0	1	y	obstructive jaundice
Phenelzine (Nardil)	No	0	1	y	elevated liver transaminases,fatal progressive necrotizing hepatocellular damage, jaundice (AR)
Phenobarbital	Yes	1	2	n	
Phentermine	No	0	1	n	
Phenylpropanolamine/chlorpheniramine (Ornade)	No	0	1	n	
Piperacillin (Piperacil)	No	0	1	y	increases in liver enzymes (LDH, SGOT, SGPT), hyperbilirubinemia, cholestatic hepatitis (AR)
Piroxicam (Feldene)	No	0	1	y	NSAID class labeling - elevations of one or more liver tests, rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (P, AR)
Potassium replacement	No	0	4	n	
Prednisone/Solu-Cortef	No	0	7	y	labeling not readily available,only hepatomegaly noted in Micromedex
Promethazine (Phenergan)	Yes	2	4	y	cholestatic jaundice (W, AR)
Propranolol	No	0	1	n	
Quetiapine (Seroquel)	Yes	1	1	y	elevations in serum transaminases (primarily ALT) (P, AR) and GGT (AR)
Quinine	No	0	1	n	
Raloxifene (Evista)	Yes	1	0	n	
Ranitidine (Zantac)	Yes	1	4	y	hepatocellular, cholestatic, or mixed hepatitis, with or without jaundice, in rare circumstances death has occurred. Rare cases of hepatic failure have also been reported. (AR)
Rapaglinide (Prandin)	No	0	1	y	elevated liver enzymes
Risperidone (Risperdal)	No	0	1	y	Infrequent: increased SGOT, increased SGPT. Rare: hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage, jaundice (AR)
Rofecoxib (Vioxx)	Yes	1	0	y	NSAID class labeling - elevations of one or more liver tests, jaundice, severe hepatic reactions, including jaundice and cases of fatal hepatitis, have been reported with naproxen (P, AR)
Salmeterol (Serevent)	No	0	1	n	
Secobarbital (Seconal)	No	0	1	n	label not readily available, no mention of hepatotoxicity in Micromedex
Sertraline (Zoloft)	Yes	1	1	y	Rare: abnormal hepatic function (AR)
Sildenafil (Viagra)	Yes	1	0	y	Abnormal liver function tests (AR)
Simvastatin (Zocor)	Yes	3	1	y	inc LFT (W) hepatitis,cholestatic jaundice, fatty change in liver, and, rarely, cirrhosis, fulminant hepatic necrosis, and hepatoma (AR)
Sirolimus (Rapamune)	Yes	1	0	y	liver function tests abnormal (P)
St. Johns Wort	No	0	1	n	
Stavudine (Zerit)	No	0	1	y	Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including stavudine and other antiretrovirals (W) elevated LFTs and hepatic steatosis, hepatitis and liver failure (AR)
STI571	Yes	1	0	unk	
Sucralfate (Carafate)	No	0	2	n	
Sumatriptan (imitrex)	No	0	1	y	disturbance of liver function tests (AR)
Tamoxifen (Nolvadex)**	Yes	1	0	y	Liver cancer, and on rare occasions, a spectrum of more severe liver abnormalities including fatty liver, cholestasis, hepatitis and hepatic necrosis, fatalities (W), changes in liver enzyme levels (W, AR)
Tamsulosin (Flomax)	Yes	1	0	n	
Terazosin (Hytrin)	No	0	2	n	

Product	Cosuspect	cos #†	conc #‡	Labeled *	labeled hepatic reaction
Theophylline	No	0	4	n	
Thioridazine (Mellaril)	No	0	1	y	Label not readily available, the following information was found in Micromedex: Nearly all the phenothiazines have been associated with the picture of cholestatic jaundice or mixed cholestatic-hepatocellular jaundice.
Thyroid replacement	No	0	8	n	
Ticlodipine (Ticlid)	No	0	1	y	Increased LFT and enzymes (P), abnormal liver test, hepatitis, hepatocellular jaundice, cholestatic jaundice, hepatic necrosis, hepatic failure (AR)
Tramadol (Ultram)	Yes	2	2	y	hepatitis (AR)
Trazodone (Desyrel)	No	0	3	y	Hepatic effects of trazodone therapy voluntarily reported to the manufacturer include CHOLESTASIS, HYPERBILIRUBINEMIA, JAUNDICE, and LIVER ENZYME ALTERATIONS (Prod Info Desyrel(R), 1998)
Triamcinolone	No	0	1	n	
Trihexyphenidyl (Artane)	No	0	1	n	
Trimethoprim/ Sulfamethoxazole	No	0	2	y	Hepatitis (including cholestatic jaundice and hepatic necrosis), elevation of serum transaminase and bilirubin (AR)
Trimipramine (Surmontil)	No	0	1	y	Jaundice (simulating obstructive); altered liver function (AR)
Ursodiol (Actigall)	No	0	1	n	label not readily available, Micromedex did not list hepatotoxicity
Valproic Acid**	Yes	1	1	y	HEPATIC FAILURE (BB, W, P)
Venlafaxine (Effexor)	Yes	1	2	y	hepatitis, jaundice, hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver) (AR)
Verapamil	Yes	1	3	y	Elevations of transaminases with and without concomitant elevations in alkaline phosphatase and bilirubin have been reported (W, AR)
Warfarin (Coumadin)	Yes	2	2	y	severe hepatic injury (W),hepatitis, cholestatic hepatic injury, jaundice, elevated liver enzymes (AR)
Zanamivir (Relenza)	Yes	1	0	n	
Zidovudine (Retrovir)	No	0	1	y	severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination, including Retrovir and other antiretrovirals (BB, W)
Zileuton (Zyflo)	Yes	1	0	y	elevation of liver enzyme levels (P, AR) jaundice, hepatitis (AR)
Zolpidem (Ambien)	No	0	4	y	Infrequent: abnormal hepatic function, inc SGPT. Rare: bilirubinemia, inc SGOT (AR)
Ingredients commonly found in acetaminophen combination products					
Diphenhydramine				n	
Hydrocodone				n	
Oxycodone				n	
Propoxyphene				y	Propoxyphene therapy has been associated with abnormal liver function tests and, more rarely, with instances of reversible jaundice (including cholestatic jaundice) (AR)
Pseudoephedrine				n	

BB=black box, W=warning, P=precautions, AR=adverse reactions, C=contraindications

† Number of reports with product listed as co-suspect medication.

‡ Number of reports with product listed as co-suspect medication.

*was unable to retrieve labels for all products, hepatotoxicity information was based on PDR (if available) or Micromedex.

**Co-suspect medications that have labeled warnings (including black box warnings and excluding class labeling) for hepatic failure or hepatic fatalities.

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/s/

Claudia Karwoski
8/2/02 07:57:10 AM
PHARMACIST

Julie Beitz
8/5/02 04:27:55 PM
DIRECTOR